

**Prophylactic Acetaminophen or Ibuprofen Result in Equivalent Acute Mountain
Sickness Incidence at High Altitude: A Prospective Randomized Trial**

Running Head: Pharmacological prevention of acute mountain sickness

Nicholas C. Kanaan¹, Alicia L. Peterson², Matiram Pun³, Jennifer Starling⁴, Bikash
Bashyal⁵, Thomas F. Freeman⁶, Jessica R. Gehner⁷, Peter S. Holck⁸, Linda Keyes⁹, Dana
R. Levin¹⁰, Catherine J. O’Leary¹¹, Katherine E. Stuart¹², Ghan B. Thapa¹³, Aditya
Tiwari¹⁴, Jared L. Velgersdyk¹⁵, Ken Zafren¹⁶, and Buddha Basnyat¹⁷

1. Nicholas C. Kanaan MD, University of Utah, Division of Emergency Medicine
2. Alicia L. Peterson MD, University of Utah, Division of Emergency Medicine
3. Matiram Pun MD, Institute of Medicine, Maharajgunj, Kathmandu, Nepal
4. Jennifer Starling MD, Denver Health, Department of Emergency Medicine
5. Bikash Bashyal MD, Institute of Medicine, Maharajgunj, Kathmandu, Nepal
6. Thomas F. Freeman MD, Augusta University, Georgia, Department of Emergency
Medicine
7. Jessica R. Gehner MD, Virginia Tech Carilion, Emergency Medicine Residency
8. Peter S. Holck PhD, University of Hawaii
9. Linda Keyes MD, University of Colorado, Aurora, CO
10. Dana R. Levin MD, University of Texas Medical Branch, Department of Aerospace
Medicine

- 1 11. Catherine J. O'Leary MD, Thomas Jefferson University Hospital, Department of
2 Emergency Medicine
- 3 12. Katherine E. Stuart MD, Queen's University, Kingston ON Canada, Department of
4 Emergency Medicine
- 5 13. Ghana B. Thapa MD, Institute of Medicine, Maharajgunj, Kathmandu, Nepal
- 6 14. Aditya Tiwari, MD, Institute of Medicine, Maharajgunj, Kathmandu, Nepal
- 7 15. Jared L. Velgersdyk MD, University of North Dakota, Department of Internal
8 Medicine
- 9 16. Ken Zafren MD, Stanford University Medical Center, Stanford, CA and Himalayan
10 Rescue Association
- 11 17. Buddha Basnyat, MD, Oxford University Clinical Research Unit, Kathmandu, Nepal
12 and Himalayan Rescue Association
13
14
15
- 16 **Corresponding author contact information:**
- 17 Buddha Basnyat, MD
- 18 Address: Nepal International Clinic, Lal Durbar Marg-48, Kathmandu, Nepal
- 19 Email: buddha.basnyat@ndm.ox.ac.uk
- 20 Phone: 977 1 4434642

1 **Abstract**

2 **Background:** Recent trials have demonstrated the usefulness of ibuprofen in the
3 prevention of acute mountain sickness (AMS), yet the proposed anti-inflammatory
4 mechanism remains unconfirmed.

5 **Objectives:** Acetaminophen and ibuprofen were tested for AMS prevention. We
6 hypothesized that a greater clinical effect would be seen from ibuprofen due to its anti-
7 inflammatory effects compared with acetaminophen's mechanism of possible symptom
8 reduction by pre-dominantly mediating nociception in the brain.

9 **Methods:** A double-blind randomized trial was conducted testing acetaminophen versus
10 ibuprofen for the prevention of AMS. A total of 332 non-Nepali participants were
11 recruited at Pheriche (4371m) and Dingboche (4410m) on the Everest Base Camp trek.
12 The subjects were randomized to either acetaminophen 1000mg or ibuprofen 600mg TID
13 until they reached Lobuche (4940m) where they were reassessed. The primary outcome
14 was AMS incidence measured by the Lake Louise Questionnaire (LLQ) score.

15 **Results:** Data from 225 subjects who met criteria were analyzed. Twenty-five
16 participants (22.1%) in the acetaminophen group, and 18 (16.1%) in the ibuprofen group
17 developed AMS ($p=0.235$). The combined AMS incidence was 19.1% (43 participants),
18 15 percentage points less than the expected AMS incidence of untreated trekkers in prior
19 studies at this location, suggesting both interventions reduced the incidence of AMS.

20 **Conclusion:** We found little evidence of any difference between acetaminophen and
21 ibuprofen groups in AMS incidence. This suggests that AMS prevention may be
22 multifactorial, affected by anti-inflammatory inhibition of the arachidonic-acid pathway
23 as well as other analgesic mechanisms that mediate nociception. Further study is needed.

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2 **Key Words:** Nepal, altitude illness, Everest, prevention, drug trials, ibuprofen,

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22 **Introduction:**

Increasing numbers of people are visiting elevations greater than 2,500 meters around the globe. Individuals who ascend to high altitude and fail to acclimatize can suffer from altitude illness, including acute mountain sickness (AMS) characterized by the constellation of symptoms: headache, fatigue, gastrointestinal upset, dizziness, and poor sleep^{1,2}. These symptoms can be self-assessed and severity of illness standardized with the Lake Louise Questionnaire (LLQ)³. A diagnosis of AMS is made when the LLQ is 3 or greater, in the presence of a headache. Along the trekking path to Everest Base Camp (EBC), the prevalence of AMS ranges from 25% to 53%^{4,5}. AMS is often preceded by High Altitude Headache (HAH), which is described as headache upon ascent to high altitude in the absence of any other AMS symptoms. Although timing of altitude illness is highly variable, it often presents within the first 24 hours of arrival to high altitude. If AMS is ignored, it can progress to dangerous and often fatal neurological and/or pulmonary conditions termed high altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE). Left untreated, HACE can lead to death within 24-48 hours⁶, thus highlighting the importance of the prevention of AMS. The best prevention of altitude illness is a slow ascent⁷. However, proper acclimatization might be ignored or deemed impractical by mountain climbers, hikers, local pilgrims, rescue teams, or military operations.

Acetazolamide is a carbonic anhydrase inhibitor considered the gold standard for prophylaxis. It can help an individual acclimatize quicker and reduce the incidence of AMS^{7,8}. Due to its side effects, potential allergies, and status as a prescription medication, alternative drugs for the prevention of AMS have been sought.

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2 The exact mechanism causing AMS is still not fully understood ⁹. However, evidence
3 points to a process in the central nervous system increasing expression of vascular
4 endothelial growth factors (VEGF), causing vasogenic edema in the brain and disruption
5 of the blood brain barrier ^{10,11}. Early cerebral inflammation due to hypobaric hypoxia has
6 also been shown to trigger an inflammatory cascade resulting in the formation of
7 arachidonic acid (AA) metabolites (thromboxanes, prostacyclin, and prostaglandins) as
8 well as serotonin, histamine, and nitric oxide and bradykinin ¹².

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10 The proposed mechanism for ibuprofen in AMS prophylaxis is through inhibiting
11 cyclooxygenase (COX) at the rate-limiting step in the inflammatory cascade, reducing
12 AA metabolites. The efficacy of dexamethasone, a steroidal anti-inflammatory
13 medication, in the prevention and treatment of AMS and HACE ⁹ provides a basis for the
14 theory that the inflammatory pathway plays a major part in the pathogenesis and
15 treatment of AMS. Three randomized controlled trials have shown the usefulness of
16 ibuprofen (600 mg TID) in the prevention of AMS ¹³⁻¹⁵. The response in AMS prevention
17 to Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and steroids provides indirect
18 evidence for a causal relationship between inflammation and altitude illness. Two studies
19 have proven the efficacy of ibuprofen in the treatment of HAH ^{16,17}. One of these studies
20 ¹⁷ with a small sample size found acetaminophen to be as effective as ibuprofen in the
21 treatment of HAH. However we found no study in the literature which investigated the
22 efficacy of acetaminophen in the prevention of AMS.

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One must also consider that headaches in AMS are multifactorial, with various chemical and mechanical factors activating a final common pathway – activation of the trigeminovascular system. The role of drugs such as acetaminophen, which primarily provide analgesia (with little anti-inflammatory effect) is unclear in the prevention of AMS. Directly comparing acetaminophen to ibuprofen for the prevention of AMS would help better understand these relationships and potentially the underlying pathophysiology. Therefore, this study was designed as a double blind, randomized, prospective clinical trial comparing ibuprofen (600 mg TID) and acetaminophen (1,000 mg TID) in the prevention of AMS in non-Nepali trekkers in the Himalayas. We chose this dose based on precedent¹⁷, as well as effective pharmacological dosing, avoiding maximum doses to minimize side effects.

Methods:

A total of 332 non-Nepali volunteers aged 18 to 65 were recruited at Pheriche (4371 m) and Dingboche (4410 m) along the Everest trekking route in the Khumbu region of Nepal. Subjects were recruited with flyers and door-to-door recruitment at the guesthouse hotels in which they stayed in Pheriche and Dingboche. Informed written consent was obtained, and participants were randomized to treatment group by a computer-generated program prepared in advance and held in a sealed envelope by an independent physician in the event of an emergency. Participants and researchers were blinded to the treatment group and group allocation. Each participant received seven doses of visually matched capsules (Jolley's Compounding Pharmacy, Salt Lake City, UT) containing either ibuprofen 600 mg or acetaminophen 1,000 mg. The medication dosing and frequency was

chosen to approximate prior studies, maintain visual similarities and blinding, and provide effective dosing.

Participants were excluded if upon enrolment they met criteria for AMS diagnosis (LLQ ≥ 3 with headache), oxygen saturation (SpO₂) less than 75%, or had spent more than 24 hours at altitudes greater than 4500 m in the preceding 9 days. They must not have taken acetaminophen, aspirin, NSAIDs, steroids, acetazolamide, diuretics, theophylline or other drugs for the prevention or treatment of AMS within the previous 48 hours. Participants were screened and excluded for a history of cardiac, pulmonary, neurological, gastrointestinal, renal, or hepatic disease. Participants who had allergies to study medications, were thought to be pregnant, or unable to consent in English were also excluded. Nepalis were not included as most of them would have been well-acclimatized guides or porters who would be doing this trek for the second or third time in the season.

Participants were instructed to take their study medication three times daily beginning the night of enrolment (day 1). On day 2, participants acclimatized to the enrolment site and slept at the same altitude. Participants took a minimum of 3 doses at the baseline altitude before proceeding on their trek. The third day, participants continued trekking, gaining approximately 550m elevation en route to Lobuche (4940 m), and took their seventh and final medication dose that night. The morning of the fourth day participants filled out their follow-up survey on AMS symptoms prior to continuing on their trek. Participants were free to determine their rate of ascent. The baseline and repeat assessment included a self-reported LLQ³, SpO₂ via pulse oximetry (Nonin Onyx II, Plymouth, MN) and rating

of headache severity on a visual analog scale (VAS). Demographics, ascent profile, compliance, and side effects were also recorded.

A priori sample size calculation suggested 230 participants (115 per arm) would be adequate to detect a difference in AMS incidence between treatment arms ($\alpha = 0.05$, $\beta = 0.8$) using aggregated historical data of 33% AMS incidence in placebo groups at the study site^{13 14,18,19}.

Analysis using both univariate (Wilcoxon rank sum, Fisher's exact, and chi-squared tests) and multivariate (linear and logistic) methods were performed by a statistician (PH) blinded to grouping, with significance reported at $p < 0.05$ using R Statistical Software (www.r-project.org). The predetermined primary end point was the incidence of AMS. Secondary end points were AMS severity (by LLQ score) and incidence and severity of headache. Ethics approval was obtained from the Nepal Health Research Council (Approval # 2071-3-16) and the trial was registered on www.clinicaltrial.gov (NCT02244437).

Results:

A total of 332 participants were consented, enrolled, and randomized to the two intervention groups: acetaminophen (A) and ibuprofen (B). Upon enrolment, 42 were excluded by pre-determined criteria. Of the remaining 290 participants, 41 (14%) were lost to follow-up and 24 (8%) were non-compliant with study protocols (by taking non-

1 study medications such as acetazolamide, or missing more than 2 doses of study
2 medications), leaving a population of 225 that were analyzed. The two groups were
3 similar to each other with regards to demographics or questionnaire results at enrolment,
4 aside from home altitude [Table 1]. The mean number of ‘missed capsules’ during the
5 ascent is also included in Table 1. The ascent profile, compliance, and side effects were
6 also recorded and there were no significant differences except for different distribution of
7 home altitude.

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9 Twenty-five participants (22.1%) in the acetaminophen group, and 18 (16.1%) in the
10 ibuprofen group developed AMS during the study period, however this difference is not
11 statistically significant ($p = 0.235$). Ibuprofen showed an observed absolute risk reduction
12 in AMS incidence of 6.2% (95% CI -4.03% to 16.53%), not significantly different from
13 zero. AMS severity at Lobuche was also not significantly different between
14 acetaminophen (mean LLQ = 2.2) and the ibuprofen groups (mean LLQ = 1.9), a
15 reduction that was also not statistically different from zero ($p=0.24$).

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17 In total, 43 participants (19.1%) developed AMS. Severe AMS (LLQ greater than 5) was
18 diagnosed in 4 (1.7%) participants in the acetaminophen group, and 4 (1.7%) in the
19 ibuprofen group, without development of HACE or HAPE. There were no adverse events
20 or medication side effects reported by participants in the questionnaire, and no patients
21 presented to the local medical clinic with any study medication related complaints during
22 the study or up to two weeks after its conclusion. Outcome measures are shown for the
23 two drugs in Table 2. Figure 2a reveals the LLQ score for the two medications in

Lobuche and Figure 2b shows the LLQ score distribution in only the participants diagnosed with AMS at Lobuche.

Although there was no difference in the severity of AMS at Lobuche in the participants using the two medications, the severity of headache (defined as LLQ headache subgroup score ≥ 2) revealed a statistically significant reduction in the ibuprofen group (n=3, 2.5%) versus acetaminophen group (n=12, 10.6%) (Table 2). However, headache severity at Lobuche as measured on a visual analog scale (VAS) was similar in both groups with mean VAS 1.8 mm for acetaminophen and 1.2 mm for ibuprofen (p=0.20). Oxygen saturation (SpO₂) change from enrolment to Lobuche was reduced more in the acetaminophen group (5.0%) than in the ibuprofen group (3.2%) (p=0.01).

Subgroup analysis (Table 3) of each LLQ symptom score was evaluated to better understand any potential differences between interventions on individual symptoms of AMS. No statistically significant changes were noted between acetaminophen and ibuprofen groups in the distribution of LLQ symptom scores: headache, gastrointestinal upset, fatigue and weakness, dizziness and lightheadedness, or difficulty sleeping.

Multivariate analyses of outcomes adjusting for sex, age, race, prior AMS exposure, altitude of residence, and compliance provided similar conclusions to the above univariate analyses.

1 **Discussion:**

2 The results of this study found no significant difference in the incidence and severity of
3 AMS between prophylactic dosing of acetaminophen and ibuprofen. The combined group
4 incidence of AMS was 19.1%, which is notably lower than the 33% averaged historical
5 incidence reported from placebo groups in prior studies at the same altitude and location
6 using similar methodology and ascent rates ^{13,14,18,19}. These results suggest that
7 acetaminophen performs similarly to ibuprofen in the prevention of AMS in partially
8 acclimatized subjects. We hypothesize that the basis of this performance is probably not
9 the arachidonic acid prostaglandin pathway but through other predominantly “non-
10 antiinflammatory” mechanisms which acetaminophen may use to influence nociception in
11 the brain. For example, axons of the trigeminal nerve (which innervate the meninges of
12 the brain) contain pain receptors ²⁰ which may be inhibited by acetaminophen.

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14 Both drugs have analgesic properties, and this raises the question whether the analgesic
15 effect of headache reduction is the main factor. In their study Lipman et al ¹⁵ provided a
16 subgroup analysis of LLS, noting no significant difference between ibuprofen and
17 placebo groups in the LLQ symptom scores of headache, fatigue, dizziness, and poor
18 sleep. Similarly in our present study of subgroup analysis (Table 3), there were no
19 differences in the subgroup analysis. This suggests that the reduction in the incidence of
20 AMS by acetaminophen and ibuprofen are due to a class effect applied to all variables,
21 and not just a reduction in headache scores.

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23 There was a trend throughout the results showing better outcomes in the primary and
24 secondary outcomes in the ibuprofen group compared with the acetaminophen group.

1 ibuprofen group had lower AMS incidence by 6.2%, lower AMS severity by LLQ score
2 by 0.3 points, and lower headache severity by VAS by 0.7 mm compared to the
3 acetaminophen group – all of which were not statistically significant reductions. While
4 the small observed differences between the two treatment groups were not significantly
5 significant, it is worthwhile to keep in mind that the study was not powered to detect
6 small differences; thus small, real differences may indeed exist between the two
7 treatment groups. The only significant difference was ibuprofen showed a smaller
8 reduction in oxygen saturation by 1.8% from baseline to study endpoint in Lobuche
9 (4940 m) which was also noted in the previous study using ibuprofen ¹⁴. The clinical
10 significance of this latter finding is limited.

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12 Finally, although there was only a trend toward lowered headache severity in the
13 ibuprofen group using the VAS scale, there was a significantly lower headache severity
14 in the ibuprofen treatment group (using the LLQ headache subgroup score) suggesting
15 that for the headache component of AMS diagnosis, ibuprofen may be more effective
16 than acetaminophen.

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19 **Limitations:**

20 Comparison of acetaminophen and ibuprofen to the standard for AMS prophylaxis,
21 acetazolamide, may have helped better define the relative efficacies of ibuprofen and
22 acetaminophen. Instead, with two interventional arms and no placebo, this study was
23 designed to maximize the possibility of detecting a significant difference in the effects of

1 acetaminophen and ibuprofen at altitude with the sample size available. No such
2 differences were observed.

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4 A placebo control group comparison, rather than prior study historical data, would have
5 improved our ability to evaluate the comparative efficacies of these two medications
6 relative to no treatment at all. Due to logistic difficulties and resource limitations, we
7 attempted to maximize our data collection and sample size to detect differences between
8 treatment groups acetaminophen and ibuprofen. As such, we chose not to add a placebo
9 arm as it would require a larger sample size than we could obtain during the trekking
10 season, and instead utilized AMS incidence among placebo groups from prior studies as a
11 comparison. Similarly, an acetazolamide study arm would have been a useful comparator,
12 but also was not feasible. Future studies examining inflammatory markers could further
13 help determine the mechanism of action of these medications.

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15 Other limitations of this study were that participants are recruited at elevation >4,000 m,
16 and have already begun the acclimatization process during their prior days of trekking
17 from their starting elevation of 2,860 m at the town of Lukla. Finally, it is worth noting
18 that although this study did not detect differences in the efficacies of ibuprofen and
19 acetaminophen for most outcomes, a larger sample may be able to conclude that small
20 differences similar to what were observed in this study are in fact statistically significant.
21 That said, the sample size utilized was adequate to allow us to conclude that any
22 differences, should they exist, are likely small and of questionable clinical importance.

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2 **Conclusion:**

3 This double-blind randomized trial comparing acetaminophen 1000mg TID and
 4 ibuprofen 600mg TID for the prevention of AMS in 225 trekkers on ascent to 4940 m
 5 along the Everest Base Camp trekking route in Nepal detected no statistically significant
 6 difference in the incidence and severity of AMS. This finding suggests that the
 7 pathophysiology of AMS may not only be dependent on arachidonic-acid pathway and
 8 inflammation but also other mechanisms that mediate nociception influenced by
 9 acetaminophen.

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 14 Rescue Association and all the participants in this study. We would also like to thank the
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17

18 **Author Contributions:**

19 BB, NK, PH, MP, and KZ conceived the idea and designed the study, and obtained ethics
 20 approval. AP, JS, TF, DL, CO, AP, BBash, KS, GT, AT, and JV participated in data
 21 collection and initial analyses. JS and LK provided field supervision. PH provided
 22 statistical analysis and writing. NK, AP, JS, TF, PH, DL, CO, KS, JV, AW, and BB

1 wrote the manuscript. All authors were involved in revising and approving the final draft
2 of the manuscript.

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6 **Disclosures:**

7 None

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